

Engineering the human thymic microenvironment to support thymopoiesis in vivo.

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Authors:	Brile Chung, Amelie Montel-Hagen, Shundi Ge, Garrett Blumberg, Kenneth Kim, Sam Klein, Yuhua Zhu, Chintan Parekh, Arumugam Balamurugan, Otto O Yang, Gay M Crooks
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Public Summary:

A healthy immune system produces T cells that can recognize and react against foreign molecules (antigens) to protect against infection, while leaving normal host cells with "self antigens" undamaged. All T cells are produced in the thymus from blood stem cells that migrate from the bone marrow. "Tolerant" T cells are those that have been "educated" to not react against self antigen on host cells. The key cells in the thymic microenvironment that control T cell production and tolerance are the thymic epithelial cells (TECs). When TECs are lost or become dysfunctional, T cell production is poor and patients are at risk for a wide range of infections. When tolerance is lost, T cells react to host tissues as if they were foreign, producing inflammation and damage and causing autoimmune diseases such as Type I Diabetes, multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus. The goal of these studies was to develop a method for engineering and transplanting new, healthy thymus tissue into patients, thus creating a way to generate healthy T cells. A major problem with regenerating the thymus ex vivo is that the TECs, which are so important for T cell growth and differentiation, tend to die during culture. We developed a method to engineer one component of the thymic microenvironment (the thymic mesenchyme) to produce specific growth factors that we propose will protect TECs. We developed specific culture conditions that allow us to grow the thymic mesenchyme separately to the TECs. The mesenchyme and TECs are then removed from culture and spun together to form a cluster of cells called a "thymic aggregate". We have shown that when we combine these thymic aggregates with cord blood stem cells (also known as "hematopoietic" stem cells) we can produce T cells from the cord blood. We can make T cells in the aggregates either in culture or after implantation of the aggregates into immune deficient mice. We have also shown that by expressing certain genes like VEGF in the aggregates we can improve engraftment and function of the implants.

Scientific Abstract:

A system that allows manipulation of the human thymic microenvironment is needed both to elucidate the extrinsic mechanisms that control human thymopoiesis, and to develop potential cell therapies for thymic insufficiency. In this report, we developed an implantable thymic microenvironment composed of two human thymic stroma populations critical for thymopoiesis; thymic epithelial cells (TECs) and thymic mesenchyme (TM). TECs and TM from postnatal human thymi were cultured in specific conditions, allowing cell expansion and manipulation of gene expression, prior to re-aggregation into a functional thymic unit. Human CD34+ hematopoietic stem and progenitor cells (HSPC) differentiated into T cells in the aggregates in vitro and in vivo following inguinal implantation of aggregates in immune deficient mice. Cord blood HSPC previously engrafted into murine bone marrow, migrated to implants and differentiated into human T cells with a broad T cell receptor repertoire. Furthermore, lentiviral-mediated expression of vascular endothelial growth factor in TM enhanced implant size and function, and significantly increased thymocyte production. These results demonstrate an in vivo system for the generation of T cells from human HSPC, and represent the first model to allow manipulation of gene expression and cell composition in the microenvironment of the human thymus. Stem Cells 2014.